REMARKS

A check for $560 for the fees for filing of an RCE ($395) and for the fee for a two-month extension of time ($225 less the $60 already paid for a one-month extension of time) accompanies this response. Any fees that may be due in connection with this application during its pendency may be charged to Deposit Account No. 06-1050. If a Petition for extension of time is needed, this paper is to be considered such Petition. An Information Disclosure Statement is filed herewith.

PENDING CLAIMS

Applicant respectfully submits that claims 1-54, 58-60, 63-76, 86, 88-124, 127-144 are pending in this application. The Advisory Action, mailed September 12, 2005, incorrectly states the pending claims. Under Section 7, the Advisory Action states that claims 1-55, 58-76, 86 and 88-144 are rejected. Applicant respectfully submits that claims 61, 62, 125 and 126 are not pending in the application.

Claim 1 is amended to incorporate the limitations of dependent claim 55, which is cancelled herein. Hence, as amended herein, claim 1 is now claim 55. No new matter is added. Claim 1 as pending and as originally filed recites that each probe includes a single-stranded portion that includes a variable region. For example, claim 1 as originally filed recites:

> 1. A method for sequencing a target nucleic acid, comprising the steps of:
>
> providing a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid;
>
> hybridizing the set to an array of nucleic acid probes to form a target array of nucleic acids, wherein each probe comprises a single-stranded portion comprising a variable region; and
>
> determining molecular weights for nucleic acids of the target array; whereby the sequence of the target nucleic acid is determined.

Therefore, "probes with a single-stranded variable region" is an original element of claim 1 and is not new matter nor an element added by amendment. Claim 1 is amended herein to incorporate the limitation of original dependent claim 55. This limitation is that the array of probes includes sufficient sequence diversity in the variable regions of the probes to hybridize to all of the target sequence. This limitation is an original element of claim 55. Claim 55, as pending and as originally filed, recites:

> 55. The method of claim 1, wherein the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination.

Thus, claim 1 is amended herein to incorporate all of the elements of pending claim 55. Therefore, no new matter is added.

Response to Examiner's Arguments in the Advisory Action

The Examiner states that the previous amendment was not entered because the limitation added to claim 1 in the Amendment After Final potentially is new matter. The Examiner states that the limitation did not come from claim 55 because claim 55 allegedly "does not teach probes with a single-stranded variable region." The applicant respectfully disagrees. Claim 55 depends from claim 1 and includes every limitation thereof. Claim 1 as pending and as originally filed recites that each probe includes a single-stranded portion that includes a variable region. Thus, "probes with a single-stranded variable region" is an original element of claim 1 and therefore an element of dependent claim 55.

Applicant respectfully submits that "probes with a single-stranded variable region" is not the element that was to added by the amendment. In the Amendment After Final, claim 1 was amended to more distinctly claim the subject matter and to include the limitation of pending claim 55. The amendment sought to incorporate from dependent claim 55 the element that the array of probes includes sufficient sequence diversity in the variable regions of the probes to hybridize to all of the target sequence. Hence, contrary to the Examiner's allegation, the limitation sought to be introduced into claim 1 by amendment in the previous response is derived from claim 55. Because "probes with a single-stranded variable region" is an original element of claim 1, and the element that the array of probes includes sufficient sequence diversity in the variable regions of the probes to hybridize to all of the target sequence is an original element of dependent claim 55, incorporating the element of dependent claim 55 into independent claim 1 does not constitute new matter.

RESPONSE TO THE OFFICE ACTION, MAILED APRIL 18, 2005

THE REJECTION OF CLAIMS 1-27, 29-33, 35-37, 40-52, 54, 61, 62, 64-70 AND 73-76 UNDER 35 U.S.C. §102(a)

Claims 1-27, 29-33, 35-37, 40-52, 54, 64-70, 73-76 and 127 are rejected under 35 U.S.C. § 102(a) as anticipated by Köster (WO 94/16101 (July 21, 1994)) because Köster allegedly discloses a method for sequencing a target nucleic acid that includes every element as claimed. This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990); *In re Bond*,

15 USPQ 1566 (Fed. Cir. 1990); *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl. 1966). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover, it is incumbent on the Examiner to identify where each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Claim 1 is directed to a method for sequencing a target nucleic acid that includes as steps providing a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid; hybridizing the set of nucleic acid fragments to an array of nucleic acid probes to form a target array of nucleic acids, where each probe includes a single-stranded portion including a variable region such that each member of the set hybridizes to a member of the array of probes; and the array includes a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination; determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid. Claims 2-27, 29-33, 35-37, 40-52, 54, 64-70, 73-76 depend from claim 1 and are directed to various embodiments thereof.

Claim 127 is directed to a system that includes a mass spectrometer, a computer and the array of claim 124. Claim 124 is directed to an array of nucleic acid probes, where each probe includes a single-stranded portion and a constant double-stranded portion; each single-stranded portion includes a variable sequence; the array of probes has sufficient sequence diversity in the variable regions to hybridize to all of a target nucleic acid molecule with complete or nearly complete discrimination; the array is attached to a solid support including a matrix material that facilitates the volatilization of nucleic acids; and the array includes a nucleic acid probe having at least one mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry.

ANALYSIS

DISCLOSURE OF KÖSTER

Köster discloses using mass spectrometry to sequence nucleic acid by analysis of the nested fragments obtained by base-specific chain termination (Sanger sequencing) (see page 14, lines 28-31 and page 15, lines 34-37). Köster discloses that immobilized nested Sanger fragments can be directly ablated for mass spectrometric analysis (page 15, lines 1-4) and the sequence determined from the mass spectrum.

Differences between the claimed subject matter and the disclosure of Köster

1. Claim 1 and its dependent claims

Köster does not disclose a method of sequencing nucleic acid that includes providing an array of nucleic acid probes including a single-stranded region and a variable region, where the array of probes includes sufficient sequence diversity in the variable regions of the probes to hybridize all of the target sequence; hybridizing the set of nucleic acid fragments to the array of nucleic acid probes to form a target array of nucleic acids, where each member of the set hybridizes to a member of the array of probes; determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid.

The Examiner states that Köster does not disclose an array that includes a collection of probes with sufficient sequence diversity in the variable region to hybridize all of the target sequence (see Office Action, page 9). Applicant agrees. In addition, Köster does not disclose identifying hybridized probes in an array by determining the molecular weight of the hybridized probes. Köster does not disclose that the sequence of the target nucleic acid can be constructed by identifying the hybridized probes. The method of Köster relies on Sanger sequencing. For example, see page 11, lines 28-30, which recites:

> This invention describes an improved method of sequencing DNA. In particular, this invention employs mass spectrometry, such as matrix-assisted laser desorption/ionization (MALDI) or electron spray (ES) mass spectrometry (MS), to analyze the Sanger sequencing reactions.

Thus, Köster does not disclose every element of claim 1 and its dependent claims. Therefore, Köster does not anticipate claims 1-27, 29-33, 35-37, 40-52, 54, 64-70 or 73-76. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

2. Claim 127

The system of claim 127 is directed to a system that includes a mass spectrometer, a computer and the array of claim 124. The array of claim 124 includes as elements that each

probe includes a single-stranded portion and a constant double-stranded portion and that the array includes a collection of probes with sufficient sequence diversity in the variable region to hybridize all of the target sequence. The Examiner alleges that Köster discloses every element of the system of claim 127. The Examiner cites to page 11, lines 28-30 and page 20, lines 33-38 to support the allegation. Applicant respectfully submits that neither citation discloses every element of the system of claim 127. Köster discloses at page 11, 28-30 that:

> This invention describes an improved method of sequencing DNA. In particular, this invention employs mass spectrometry, such as matrix-assisted laser desorption/ionization (MALDI) or electron spray (ES) mass spectrometry (MS), to analyze the Sanger sequencing reactions.

Köster discloses at page 20, lines 33-38 that:

> For mass spectrometric DNA sequencing, all base-specifically terminated reactions of the four clones are pooled and mass analyzed. The various mass peaks belonging to the four dideoxy-terminated (e.g., ddT-terminated) fragment families are assigned to specifically elongated and ddT-terminated fragments by searching (such as by a computer program) for the known molecular ion peaks of UP^0, UP^1, UP^2 and UP^3 extended by either one of the four dideoxynucleoside triphosphates, UP^0-ddN^0. UP^1-ddN^0, UP^2-ddN^0 and UP^3-ddN^0.

Applicant respectfully submits that there is no disclosure in either of the cited sections of an array of nucleic acid probes, where each probe includes a single-stranded portion and a constant double-stranded portion, or an array of probes having sufficient sequence diversity in the variable regions to hybridize to all of a target nucleic acid molecule with complete or nearly complete discrimination. Further, the Examiner states in the Office Action (see Office Action, page 9) that Köster does not disclose an array that includes as elements probes that include a double-stranded portion and a single-stranded portion. The Examiner also states (*Id.*) that Köster does not disclose an array that includes a collection of probes with sufficient sequence diversity in the variable region to hybridize all of the target sequence. Applicant agrees. Thus, Köster does not disclose every element of claim 127 and, therefore, Köster does not anticipate claim 127. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

THE REJECTION OF CLAIM 28 UNDER 35 U.S.C. §103(a)

Claim 28 is rejected under 35 U.S.C. §103(a) over Köster (WO 94/16101) in view of Weiss (U.S. 6,025,193) because Köster allegedly teaches all elements of claim 28, except generation of thiol moieties by using Beucage reagent, but Weiss allegedly cures this defect.

This rejection is respectfully traversed.

RELEVANT LAW

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *see, also, In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963).

Further, that which is within the capabilities of one of ordinary skill in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

CLAIM 28

Claim 28 depends from claim 1, and is directed to an embodiment thereof where the array includes nucleic acid probes having as a mass-modifying functionality a thiol moiety that is generated by using Beucage reagent.

TEACHINGS OF THE CITED ART

Köster (WO 94/16101)

See related section above.

Weiss (U.S. 6,025,193)

Weiss teaches methods and compositions for diagnosing and treating pathological conditions related to a dopamine receptor abnormality, which includes administering a plasmid encoding an oligonucleotide anti-sense to one or more RNA molecules encoding one

of the several dopamine receptors. The reference teaches that unmodified oligodeoxynucleotides can be converted into phosphorothioate oligodeoxynucleotides using standard phosphoramidite protocols but replacing the standard oxidation by iodine with Beucage reagent for sulfurization. Weiss teaches that using Beucage reagent results in the replacement of every oxygen group of the phosphodiester bond with a sulfur group, and that such substitutions result in an asymmetric distribution of the negative charge to predominate on the sulfur atom, resulting in "improved stability to nucleases, retention of solubility in water and stability to base-catalyzed hydrolysis" (col. 13, lines 2-14), improved distribution and *in vivo* stability (col. 15, lines 41-45), and activation of Rnase H (col. 13, lines 45-47).

Weiss does not teach or suggest a method for sequencing a target nucleic acid that includes providing a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid; providing an array of nucleic acid probes comprising a single-stranded region and a variable region, where the array of probes includes sufficient sequence diversity in the variable regions of the probes to hybridize all of the target sequence; hybridizing the set of nucleic acid fragments to the array of nucleic acid probes to form a target array of nucleic acids, where each member of the set hybridizes to a member of the array of probes; determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of the teachings of Köster with the teachings of Weiss does not result in the instantly claimed methods.

As discussed above, Köster does not teach or suggest a method for sequencing a target nucleic acid that includes as elements an array that includes a collection of probes with sufficient sequence diversity in the variable region to hybridize all of the target sequence, identifying hybridized probes in the array by determining the molecular weight of the hybridized probes, and determining the sequence of the target nucleic acid by identifying the hybridized probes. Weiss does not teach or suggest a method for sequencing a target nucleic acid, or providing an array that includes a collection of nucleic acid probes with sufficient sequence diversity in the variable region to hybridize all of the target sequence, or identifying hybridized probes in an array by determining the molecular weight of the hybridized probes, or determining the sequence of the

target nucleic acid by identifying the hybridized probes. Thus, even if Weiss teaches generating thiol moieties using Beucage reagent, Weiss fails to cure the deficiencies in the teachings of Köster because Weiss does not teach or suggest the elements of the claimed subject matter missing from the teachings of Köster.

Neither Köster nor Weiss, individually or in combination, teaches or suggests a method for sequencing a target nucleic acid that includes as elements providing an array that includes a collection of nucleic acid probes with sufficient sequence diversity in the variable region to hybridize all of the target sequence, identifying hybridized probes in an array by determining the molecular weight of the hybridized probes, and determining the sequence of the target nucleic acid by identifying the hybridized probes. Thus, combining the teachings of Köster and Weiss does not result in the instantly claimed method of claim 28. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

THE REJECTION OF CLAIM 34 UNDER 35 U.S.C. §103(a)

Claim 34 is rejected under 35 U.S.C. §103 as being unpatentable over Köster (WO 94/16101) in view of Cantor (U.S. Patent 5,503,980) because Köster allegedly teaches all elements of claim 34, except ligating the hybridized target nucleic acids to the probes, but Cantor allegedly cures this defect. This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

CLAIM 34

Claim 34 depends from claim 1, and is directed to an embodiment thereof further including the step of ligating the hybridized target nucleic acids to the probes.

TEACHINGS OF THE CITED ART

Köster (WO 94/16101)

See related section above.

Cantor (U.S. Patent 5,503,980)

Cantor teaches positional sequencing by hybridization. Cantor teaches probes having a double-stranded portion, a single-stranded portion, and a random sequence within the single-stranded portion that is determinable (col. 5, lines 40-45). In one embodiment, Cantor teaches a method for determining a nucleotide sequence by positional hybridization (col. 7, lines 63 through col. 8, line 6). Cantor teaches determining a target nucleotide sequence by analyzing

the hybridization pattern of target nucleic acid fragments on a hybridization chip, which provides a fingerprint identification of the target nucleotide sequence (col. 7, lines 6-10).

Cantor does not teach or suggest a method for sequencing a target nucleic acid that includes providing an array that includes a collection of probes with sufficient sequence diversity in the variable region to hybridize all of the target sequence, identifying hybridized probes in an array by determining the molecular weight of the hybridized probes, and determining the sequence of the target nucleic acid by identifying the hybridized probes.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of prima facie obviousness for the following reasons.

The combination of the teachings of Köster with the teachings of Cantor does not result in the instantly claimed methods.

As discussed above, Köster does not teach or suggest a method for sequencing a target nucleic acid that includes as elements providing an array that includes a collection of probes with sufficient sequence diversity in the variable region to hybridize all of the target sequence, identifying hybridized probes in an array by determining the molecular weight of the hybridized probes, and determining the sequence of the target nucleic acid by identifying the hybridized probes. Cantor does not cure this defect. Cantor teaches arrays of probes that are partially double-stranded and partially single-stranded. There is no teaching or suggestion in Cantor of identifying hybridized probes in an array by determining the molecular weight of the hybridized probes, and determining the sequence of the target nucleic acid by identifying the hybridized probes. The only teachings directed to molecular weight in Cantor are the teaching in Example 2 directed to fractionation of a sample, and reference to the Maxim and Gilbert sequencing technique, where terminally labeled DNA molecules are chemically cleaved at single base repetitions and then the molecular weight of each partially cleaved fragment is determined using electrophoresis to produce a pattern of fragments on a gel, whereby the DNA sequence can be read (see col. 1, lines 24-35). Hence, Cantor does not teach or suggest determining molecular weights of nucleic acids in the target array to identify hybridized probes, and based on the hybridized probes, determining the sequence of the target nucleic acid. Hence, Cantor does not teach or suggest the subject matter missing from Köster.

Thus, even if Cantor teaches ligating the hybridized target nucleic acids to the probes, combining the teachings of Köster and Cantor does not result in a method for sequencing a target nucleic acid that includes as elements identifying hybridized probes in an array by

determining the molecular weight of the hybridized probes, and determining the sequence of the target nucleic acid by identifying the hybridized probes. Hence, the combination of Köster and Cantor does not teach or suggest every element of claim 34. Therefore, the Examiner has failed to set forth a prima facie case of obviousness. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

REBUTTAL TO EXAMINER'S ARGUMENTS

In maintaining this rejection, the Examiner alleges that Applicant's previous argument "attacked" the references individually instead of addressing the combination of the references. The Applicant respectfully disagrees. The previous response did address the combination of the teachings of the references and did not "attack" them individually. Attention is directed to the section at page 22 of the previous response with the header "ANALYSIS" and the header " The combination of the teachings of Köster with the teachings of Cantor does not result in the instantly claimed methods," which states:

> As discussed above, Köster does not teach or suggest a method for sequencing a target nucleic acid that includes as an element determining molecular weights of nucleic acids in the target array to identify hybridized probes, and based upon the hybridized probes, determining the sequence of the target nucleic acid. Cantor does not cure this defect. Cantor teaches arrays of probes that are partially double-stranded and partially single-stranded. There is no teaching or suggestion in Cantor to determine the molecular weights of nucleic acid fragments hybridized in a target array in order to identify hybridized probes and thereby determine the sequence of the target nucleic acid. The only teachings directed to molecular weight in Cantor are the teaching in Example 2 directed to fractionation of a sample, and reference to the Maxim and Gilbert sequencing technique, where terminally labeled DNA molecules are chemically cleaved at single base repetitions and then the molecular weight of each partially cleaved fragment is determined using electrophoresis to produce a pattern of fragments on a gel, whereby the DNA sequence can be read (see col. 1, lines 24-35). Hence, Cantor does not teach or suggest determining molecular weights of nucleic acids in the target array to identify hybridized probes, whereby the sequence of the target nucleic acid is determined. Hence, Cantor does not teach or suggest the subject matter missing from the teachings of Köster.
>
> Thus, even if Cantor teaches ligating the hybridized target nucleic acids to the probes, **combining the teachings of Köster and Cantor does not result in a method for sequencing a target nucleic acid that includes as a step determining molecular weights of nucleic acids in the target array to identify hybridized probes, and based upon the hybridized probes, determining the sequence of the target nucleic acid. Hence, the combination of Köster and Cantor does not teach or suggest every element of claim 34.** Therefore, the Examiner has failed to set forth a prima facie case of obviousness. Applicant respectfully requests that the rejection be reconsidered and withdrawn. [emphasis added]

Applicant respectfully submits that the individual references were not "attacked," but instead the references were analyzed to show that the elements missing from Köster are not taught or suggested by Cantor.

THE REJECTION OF CLAIMS 71 AND 72 UNDER 35 U.S.C. §103(a)

Claims 71 and 72 are rejected under 35 U.S.C. §103 as being unpatentable over Köster (WO 94/16101) in view of Sanghvi *et al.* (U.S. Patent No. 6,214,551) because Köster allegedly teaches all elements of the claims except that the selectively releasable bond is 4,4'-dimethoxytrityl or a derivative thereof, and Sanghvi *et al.* allegedly cures this defect. The Examiner contends that Sanghvi *et al.* teaches the selectively releasable bond 4,4'-dimethoxytrityl or a derivative thereof, and argues that although the reference does not teach the derivative 3 or 4 [bis-(4-methoxy-phenyl)]-methyl-benzoic acid in particular, Sanghvi *et al.* teaches equivalent compounds and derivatives used for the same purpose. This rejection is respectfully traversed.

THE CLAIMS

Claims 71 and 72 ultimately depend from claim 1 and are directed to embodiments thereof. Claim 71 is directed to the embodiment where each probe is attached to the solid support by a selectively releasable bond that includes 4, 4'-dimethoxytrityl or a derivative thereof. Claim 72 is directed to the embodiment where the derivative of 4, 4'-dimethoxytrityl is selected from the group consisting of 3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid, N-succinimidyl-3 or 4 [bis-(4-methoxy-phenyl)]-methyl-benzoic acid, N-succinimidyl-3 or 4 [bis-(4-methoxyphenyl)]-hydroxy-methyl-benzoic acid, N-succinimidyl-3 or 4 [bis-(4-methoxy-phenyl)]-chloromethyl-benzoic acid and salts thereof.

RELEVANT LAW

See related section above.

TEACHINGS OF THE CITED ART

Köster (WO 94/16101)

See related section above.

Sanghvi *et al.* (U.S. Patent 6,214,551)

Sanghvi *et al.* teaches compounds that mimic and/or modulate the activity of wild-type nucleic acids. The compounds taught by Sanghvi *et al.* contain a selected nucleotide sequence where the nucleotides are covalently bound through linking groups that contain adjacent nitrogen atoms. Sanghvi *et al.* teaches the use of dimethoxytrityl groups as a blocking group during nucleoside polymerization. Sanghvi *et al.* teaches that an oligonucleotide is tethered to a solid support via its 3' hydroxyl group (col. 57, line 63 through col. 58, line 14).

Sanghvi *et al.* does not teach or suggest the use of dimethoxytrityl or a derivative thereof as a selectively releasable bond by which to attach a probe to a solid support. Sanghvi *et al.* does not teach or suggest using mass spectrometry, or using mass spectrometry for sequencing nucleic acids. Sanghvi *et al.* does not teach or suggest providing an array that includes a collection of probes with sufficient sequence diversity in the variable region to hybridize all of the target sequence, identifying hybridized probes in an array by determining the molecular weight of the hybridized probes, and determining the sequence of the target nucleic acid by identifying the hybridized probes.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Köster with the teachings of Sanghvi *et al.* does not result in the instantly claimed methods.

As discussed above, Köster does not teach or suggest methods for sequencing a target nucleic acid that include as elements providing an array that includes a collection of probes with sufficient sequence diversity in the variable region to hybridize all of the target sequence, identifying hybridized probes in an array by determining the molecular weight of the hybridized probes, and determining the sequence of the target nucleic acid by identifying the hybridized probes. Sanghvi *et al.* does not cure these defects. Sanghvi *et al.* does not teach or suggest providing an array that includes a collection of probes with sufficient sequence diversity in the variable region to hybridize all of the target sequence, or identifying hybridized probes in an array by determining the molecular weight of the hybridized probes, or determining the sequence of the target nucleic acid by identifying the hybridized probes. Hence, Sanghvi *et al.* does not teach or suggest the elements missing from the teachings of Köster. Accordingly, even if, arguendo, Sanghvi *et al.* teaches selectively releasable bonds containing 4,4'-dimethoxytrityl or a derivative thereof, which applicant contends Sanghvi *et al.* does not teach, the combination of Köster and Sanghvi *et al.* does not teach or suggest all the elements of the claimed methods.

Neither Köster nor Sanghvi *et al.*, alone or in combination, teaches or suggests a method for sequencing a target nucleic acid that includes as elements providing an array that includes a collection of probes with sufficient sequence diversity in the variable region to hybridize all of the target sequence, identifying hybridized probes in an array by determining the molecular weight of the hybridized probes, and determining the sequence of the target

nucleic acid by identifying the hybridized probes. Thus, combining the teachings of Köster and Sanghvi *et al.* does not result in the instantly claimed methods of claims 71 and 72. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

REBUTTAL TO EXAMINER'S ARGUMENTS

In maintaining this rejection, the Examiner alleges that Applicant's previous argument "attacked" the references individually instead of addressing the combination of the references. The Applicant respectfully disagrees. The previous response did address the combination of the teachings of the references and did not "attack" them individually. Attention is directed to the section at page 25 of the previous response with the header "ANALYSIS" and the header "The combination of the teachings of Köster with the teachings of Sanghvi *et al.* does not result in the instantly claimed methods," which states:

> As discussed above, Köster does not teach or suggest methods for sequencing a target nucleic acid that include as an element determining the molecular weight of nucleic acids in the target array to identify hybridized probes, whereby the sequence of the target nucleic acid is determined. Sanghvi *et al.* does not cure this defect. Sanghvi *et al.* does not teach or suggest using mass spectrometry, or using mass spectrometry for sequencing nucleic acids, or hybridizing a set of nucleic acid fragments containing a sequence that corresponds to a sequence of the target nucleic acid to an array of nucleic acid probes to form a target array of nucleic acids. Sanghvi *et al.* does not teach or suggest determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid. Hence, Sanghvi *et al.* does not teach or suggest the subject matter missing from the teachings of Köster.
>
> Accordingly, even if, arguendo, Sanghvi *et al.* teaches selectively releasable bonds containing 4,4'-dimethoxytrityl or a derivative thereof, which applicant contends is not taught by Sanghvi *et al.*, **the combination of Köster and Sanghvi *et al.* does not teach or suggest all the elements of the claimed methods.**
>
> Neither Köster nor Sanghvi *et al.*, alone or in combination, teaches or suggests a method for sequencing a target nucleic acid that includes as an element determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid. Thus, **combining the teachings of Köster and Sanghvi *et al.* does not result in the instantly claimed methods of claims 71 and 72.** Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness. [emphasis added]

Applicant respectfully submits that the individual references were not "attacked," but instead the references were analyzed to show that the elements missing from Köster are not taught or suggested by Sanghvi *et al.* and that combining the teachings of Köster and Sanghvi *et al.* does not result in the claimed subject matter.

THE REJECTION OF CLAIMS 38, 39, 53, 55, 58-60, 63, 86, 88-124 and 128-144 UNDER 35 U.S.C. §103(a)

Claims 38, 39, 53, 55, 58-60, 63, 86, 88-124 and 128-144 are rejected under 35 U.S.C. § 103(a) over Köster (WO 94/16101) in view of Cantor (U.S. 5,503,980), because Köster allegedly teaches all elements of the claims except probes that include a double-stranded portion and a single-stranded portion, probes having 10-1,000 nucleotides or having a variable region of about 4-20 nucleotides, arrays including 10^4 or more different members or arrays of probes having sufficient sequence diversity in the variable regions to hybridize to all of a target nucleic acid molecule with complete or nearly complete discrimination, but Cantor allegedly cures these defects. This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 1 is directed to a method for sequencing a target nucleic acid, that includes providing a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid; hybridizing the set to an array of nucleic acid probes to form a target array of nucleic acids, where each probe includes a single-stranded portion including a variable region such that each member of the set hybridizes to a member of the array of probes; determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid. Claims 38, 39, 53, 89-103, 114-124 and 128 ultimately depend from claim 1 and are directed to various embodiments thereof.

Claim 124 is directed to an array of nucleic acid probes, where each probe includes a single-stranded portion and a constant double-stranded portion; each single-stranded portion includes a variable sequence; the array of probes has sufficient sequence diversity in the variable regions to hybridize to all of a target nucleic acid molecule; the array is attached to a solid support including a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry; and the array includes a nucleic acid probe having at least one mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry. Claims 129-144 depend from claim 124 and are directed to various embodiments thereof. Claim 86 depends from claim 127, which is directed to a system including a mass spectrometer, a computer and the array of claim 124.

TEACHINGS OF THE CITED ART

Köster (WO 94/16101)

See related section above.

Cantor (U.S. Patent 5,503,980)

See related section above.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

1. The combination of the teachings of Köster with the teachings of Cantor does not result in the methods of claims 38, 39, 53, 88-110, 114-123 and 128

Claims 38, 39, 53, 55, 88-110, 114-123 and 128 ultimately depend from claim 1. As discussed above in the traverse of the rejection of claim 34 under 35 U.S.C. §103 as being unpatentable over Köster in view of Cantor, Köster does not teach or suggest a method for sequencing a target nucleic acid that includes as elements identifying hybridized probes in an array by determining the molecular weight of the hybridized probes, and determining the sequence of the target nucleic acid by identifying the hybridized probes.

Cantor does not cure these defects. Cantor does not teach or suggest identifying hybridized probes in an array by determining the molecular weight of the hybridized probes, and determining the sequence of the target nucleic acid by identifying the hybridized probes. As discussed above, the only teachings directed to molecular weight in Cantor are the teaching in Example 2 directed to fractionation of a sample, and reference to the Maxim and Gilbert sequencing technique, where the molecular weight of each partially cleaved terminally labeled DNA molecule fragment is determined using electrophoresis to produce a pattern of fragments on a gel, whereby the DNA sequence can be read (see col. 1, lines 24-35).

Thus, even if Cantor teaches probes that include a double-stranded portion and a single-stranded portion, or probes having a single stranded portion of about 4-20 nucleotides, or probes having a variable region of about 4-20 nucleotides, or arrays of probes having a variable region that is determinable, combining the teachings of Köster and Cantor does not teach or suggest every element of the subject matter of claim 1. Claims 38, 39, 53, 88-110, 114-123 and 128 ultimately depend from claim 1. Hence, the combination of the teachings of Köster and Cantor does not teach or suggest every element of the methods of claims 38, 39, 53, 88-110, 114-123 and 128. Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

2. The combination of teachings of Köster with the teachings of Cantor does not result in the arrays of claims 129-132, 134 and 136-144

Claims 129-132, 134 and 136-144 depend from claim 124, which is directed to an array of nucleic acid probes. In maintaining this rejection, the Examiner alleges that there is no limitation of "matrix material that facilitates the volatilization of nucleic acids for mass spectrometry" (Office Action, page 15). Applicant respectfully submits that the Examiner is mistaken. Claim 124 recites:

> 124. (Previously presented) An array of nucleic acid probes, wherein:
> each probe comprises a single-stranded portion and a constant double-stranded portion;
> each single-stranded portion comprises a variable sequence;
> the array of probes has sufficient sequence diversity in the variable regions to hybridize to all of a target nucleic acid molecule with complete or nearly complete discrimination;
> **the array is attached to a solid support comprising a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry** [emphasis added]; and
> the array comprises a nucleic acid probe having at least one mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry.

This element has been present in claim 124 since claim 124 originally was added in a Preliminary Amendment, mailed April 4, 2001. Köster does not teach or suggest an array of nucleic acid probes where the array is attached to a solid support including a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry.

Cantor does not cure this defect. Cantor does not teach or suggest an array of nucleic acid probes where the array is attached to a solid support that includes a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry. The only "matrix" taught be Cantor is an embodiment of the solid support itself. For example, see col. 6, line 64 through col. 7, line 1, which recites:

> Preferred examples of a solid support include a plastic, a ceramic, a metal, a resin, a gel, and a membrane. A more preferred embodiment comprises a two-dimensional or three-dimensional matrix, such as a gel, with multiple probe binding sites, such as a hybridization chip...

Thus, even if Cantor teaches a variety of lengths of probes, variable regions of probes and fragments of nucleic acids, Cantor does not teach or suggest an array or probes attached to a solid support including a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry, an element of the claimed subject matter missing from the teachings of Köster. Hence, combining the teachings of Köster and Cantor does not teach or suggest every

element of the claimed array of nucleic acid probes, which includes a solid support including a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry. Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

3. The combination of teachings of Köster with the teachings of Cantor does not result in the systems of claims 86 and 127

Claim 86 depends from claim 127, which is directed to a system including a mass spectrometer, a computer and the array of claim 124. As discussed above, the combination of the teachings of Köster and Cantor does not result in the array of claim 124. Hence, combining the teachings of Köster and Cantor does not result in the systems of claims 86 and 127, which includes the array of claim 124.

REBUTTAL TO EXAMINER'S ARGUMENTS

In maintaining this rejection, the Examiner states that "Applicant continues to argue against the references individually" (Office Action, page 14). The Applicant respectfully disagrees. Applicant respectfully submits that the rejection was traversed in three separate sections, since claims 38, 39, 53, 55, 58-60, 63, 86, 88-124 and 128-144 are directed to methods, arrays and systems. Each section of the previous response addressed the combination of the teachings of the references. The Examiner's attention is directed to the section at page 27 of the previous response with the header "ANALYSIS," which states:

> **1. Claims 38, 39, 53, 55, 88-110, 114-123 and 128 - Methods**
>
> Claims 38, 39, 53, 55, 88-110, 114-123 and 128 ultimately depend from claim 1. As discussed above in the traverse of the rejection of claim 34 under 35 U.S.C. §103 as being unpatentable over Köster (WO 94/16101) in view of Cantor (U.S. Patent 5,503,980), Köster does not teach or suggest a method for sequencing a target nucleic acid that includes as an element determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid. Cantor does not cure this defect. Cantor does not teach or suggest determining the molecular weights for nucleic acids of the target array to identify hybridized probes, whereby the sequence of the target nucleic acid is determined. **Thus, combining the teachings of Köster and Cantor does not teach or suggest the subject matter claimed in claim 1.** Claims 38, 39, 53, 55, 88-110, 114-123 and 128 ultimately depend from claim 1. **Hence, the combination of the teachings of Köster and Cantor does not teach or suggest the methods claimed in claims 38, 39, 53, 55, 88-110, 114-123 and 128.** Therefore, the Examiner has failed to set forth a prima facie case of obviousness.
>
> **2. Claims 129-132, 134 and 136-144 - Arrays**
>
> Claims 129-132, 134 and 136-144 depend from claim 124, which is directed to an array of nucleic acid probes. Köster does not teach or suggest an array of nucleic acid probes where the array is attached to a solid support including a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry.

Cantor does not cure this defect. Cantor does not teach or suggest an array of nucleic acid probes where the array is attached to a solid support that includes a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry. The only "matrix" taught be Cantor is an embodiment of the solid support itself. For example, see col. 6, line 64 through col. 7, line 1, which recites:

> Preferred examples of a solid support include a plastic, a ceramic, a metal, a resin, a gel, and a membrane. A more preferred embodiment comprises a two-dimensional or three-dimensional matrix, such as a gel, with multiple probe binding sites, such as a hybridization chip...

Hence, **combining the teachings of Köster and Cantor does not teach or suggest an array of nucleic acid probes as instantly claimed, that includes as an element that the array is attached to a solid support including a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry**. Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

3. Claims 86 and 127 - Systems

Claim 86 depends from claim 127, which is directed to a system including a mass spectrometer, a computer and the array of claim 124. As discussed above, **the combination of the teachings of Köster and Cantor does not result in the instantly claimed array of 124. Hence, combining the teachings of Köster and Cantor does not result in the systems as claimed in claims 86 and 127.** [emphasis added]

Applicant respectfully submits that the individual references were not "attacked," but instead the references were analyzed to show that the elements missing from Köster are not taught or suggested by Cantor.

* * *

In view of the above, entry of the amendment and allowance is respectfully requested.

Respectfully submitted,

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